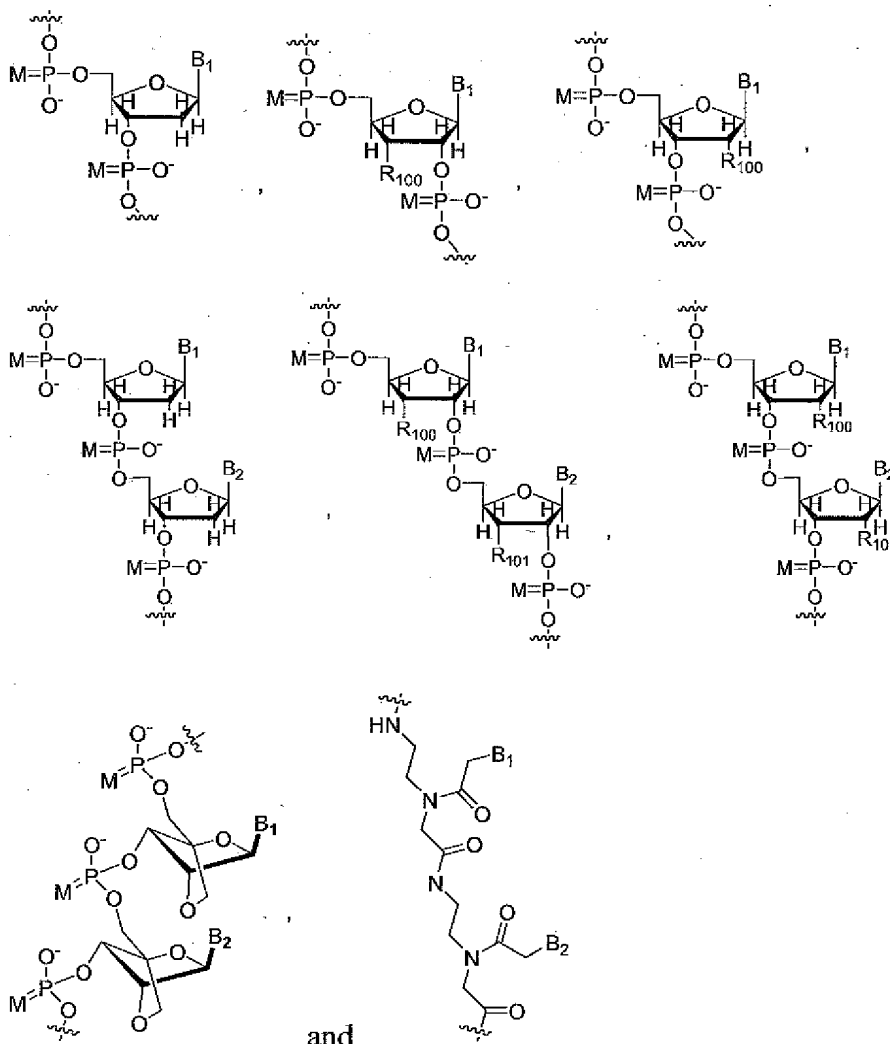


**AMENDMENTS TO THE CLAIMS**

This listing of claims will replace all prior versions, and listings, of claims in the application.

**Listing of Claims:**

1. (Cancelled)
2. (Currently Amended) The prodrug of claim 27, wherein the oligonucleotide comprises a nucleotide that is selected from the group consisting of



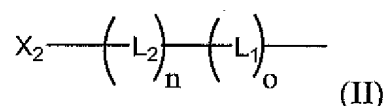
wherein

M is O or S;

B<sub>1</sub> and B<sub>2</sub> are independently selected from the group consisting of A (adenine), G (guanine), C (cytosine), T (thymine), U (uracil) and modified bases;

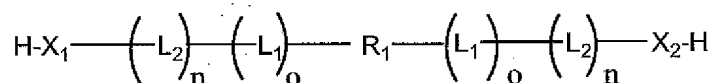
R<sub>100</sub> and R<sub>101</sub> are independently selected from the group consisting of H, OR' where R' is H, a C<sub>1-6</sub> alkyl, substituted alkyls, nitro, halo and aryl.

3. (Cancelled)
4. (Previously Presented) The prodrug of claim 2, wherein M is S.
5. (Previously Presented) The prodrug of claim 27, wherein the oligonucleotide residue is a phosphorothioate oligonucleotide residue.
6. (Previously Presented) The prodrug of claim 27, wherein said oligonucleotide residue is an antisense oligonucleotide residue or oligodeoxynucleotide residue.
7. (Currently Amended) The prodrug of claim 6, wherein said antisense oligonucleotide residue or oligodeoxynucleotide residue is selected from the group consisting of [[,]] oligonucleotides and oligodeoxynucleotides with phosphorodiester backbones or phosphorothioate backbones, LNA, PNA, tricyclo-DNA, decoy ODN, ribozymes, spiegelmers, and CpG oligomers.
8. (Previously Presented) The prodrug of claim 6, wherein said antisense oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, wherein n of SEQ ID NO: 4 is any nucleotide.
9. (Currently Amended) The prodrug of claim 27, wherein R<sub>1</sub> is a polyalkylene oxide polymeric residue having a capping group A, selected from the group consisting of OH, NH<sub>2</sub>, SH, CO<sub>2</sub>H, C<sub>1-6</sub> alkyls, and



wherein  $X_2$  is a single stranded or double stranded oligonucleotide residues,  
wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides.

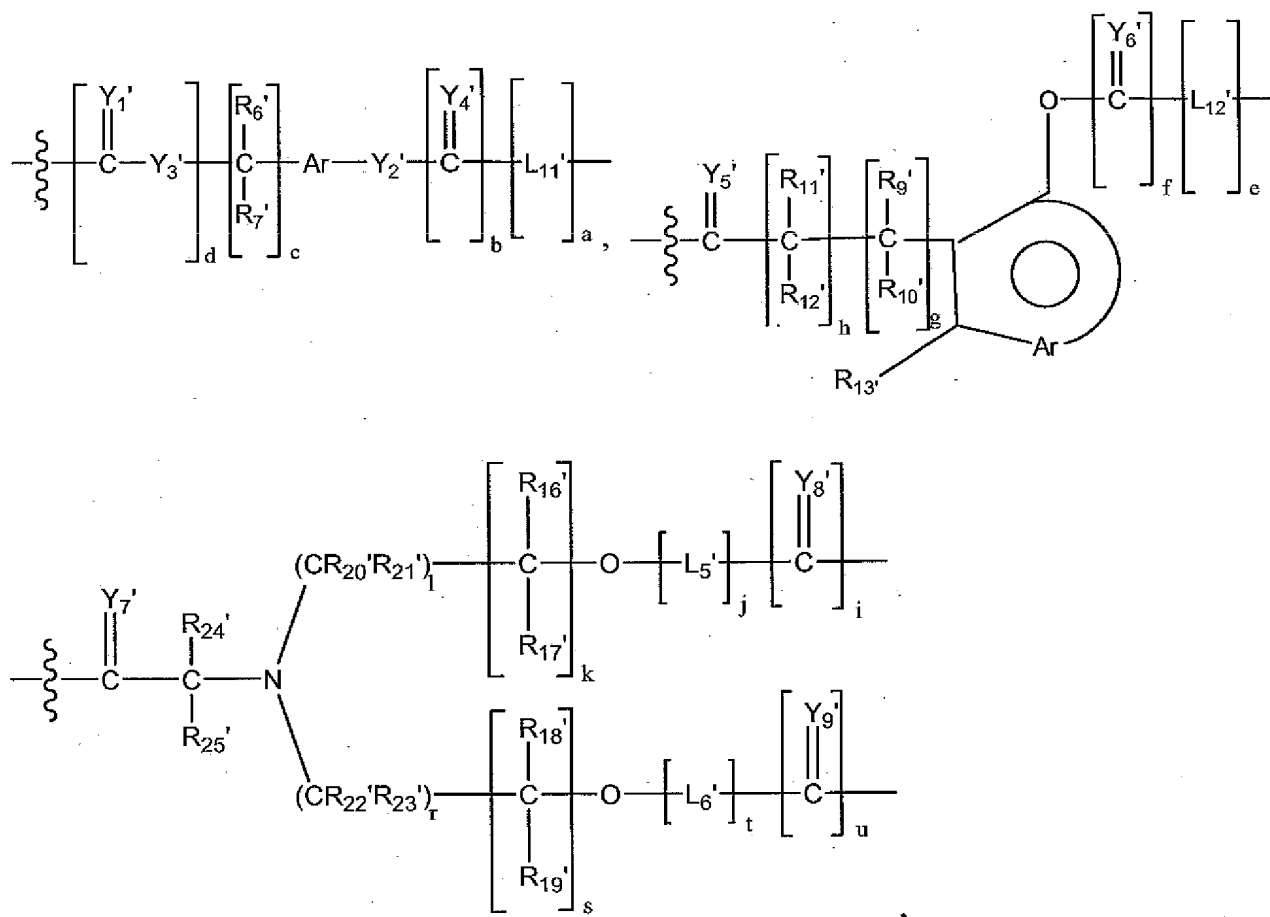
10. (Currently Amended) A prodrug of claim 9, selected from the group consisting of:

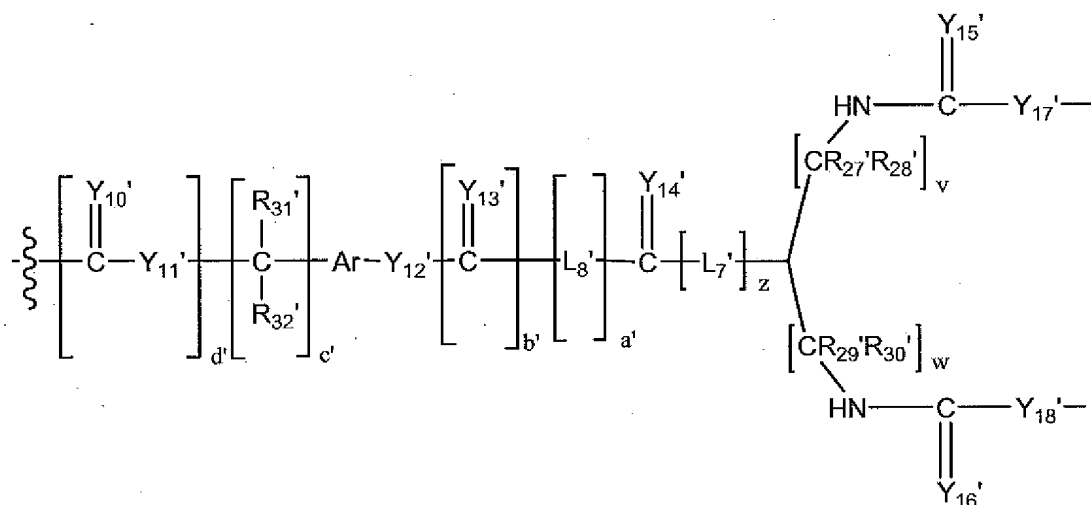


wherein each  $X_2$  is independently a 3' oligonucleotide or 5' oligonucleotide.

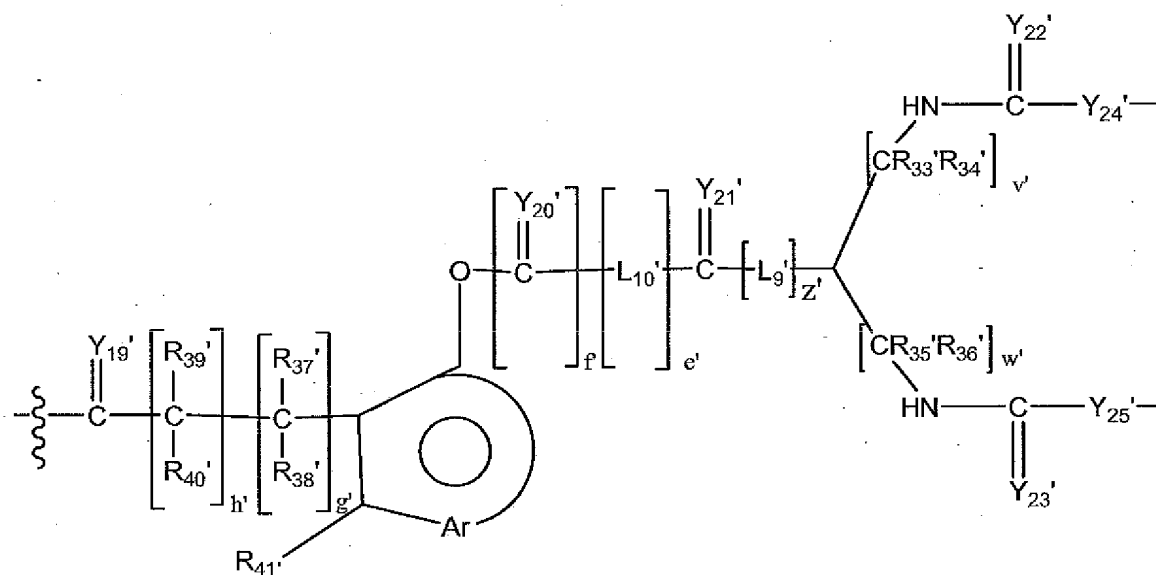
11. (Cancelled)

12. (Currently Amended) The prodrug of claim 27, wherein  $L_1$  is selected from the group consisting of:





and



wherein,

$Y_1 - Y_{25}$  are independently selected from the group consisting of O, S or  $NR_9$ ;

$R_{6'-7'}$ ,  $R_{9'-13'}$ ,  $R_{16'-25'}$ ,  $R_9$  and  $R_{27'-41'}$  are independently selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cycloalkyls, aryls, substituted aryls, aralkyls,  $C_{1-6}$  heteroalkyls, substituted  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy and  $C_{1-6}$  heteroalkoxy;

$L_{5'-12'}$  are independently selected bifunctional spacers;

Ar is a moiety which forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

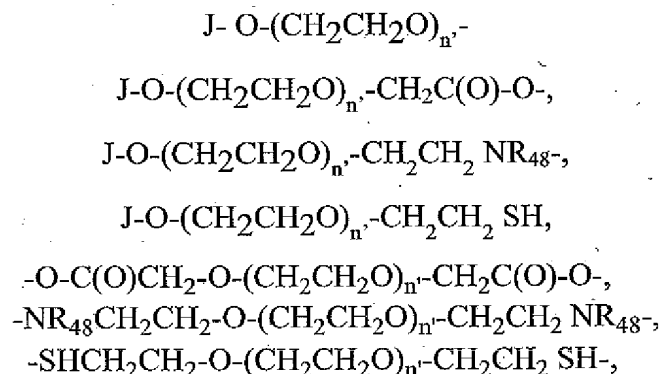
c, h, k, l, r, s, v, w, v', w', c', and h' are independently selected positive integers;

a, e, g, j, t, z, a', z', e' and g' are independently either zero or a positive integer; and  
b, d, f, i, u, b', d' and f' are independently zero or one.

13. (Cancelled)

14. (Currently Amended) The prodrug of claim 27, wherein R<sub>1</sub> is a ~~polyalkylene~~  
polyethylene glycol.

15. (Currently Amended) The prodrug of claim 27, wherein R<sub>1</sub> is selected from the  
group consisting of:



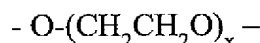
wherein

n' is the degree of polymerization;

R<sub>48</sub> is selected from the group consisting of hydrogen, C<sub>1-6</sub> alkyls, C<sub>3-12</sub> branched  
alkyls, C<sub>3-8</sub> cycloalkyls, ~~C<sub>1-6</sub> substituted alkyls, C<sub>3-8</sub> substituted cycloalkyls~~, aryls,  
~~substituted aryls, aralkyls~~; C<sub>1-6</sub> heteroalkyls, ~~substituted C<sub>1-6</sub> heteroalkyls~~, C<sub>1-6</sub> alkoxy,  
phenoxy and C<sub>1-6</sub> heteroalkoxy; and

J is a capping group.

16. (Previously Presented) The prodrug of claim 27, wherein R<sub>1</sub> comprises



wherein x is a positive integer selected so that the weight average molecular weight  
is at least about 2,000 Da to about 136,000 Da.

17. (Previously Presented) The prodrug of claim 27, wherein R<sub>1</sub> has a weight average

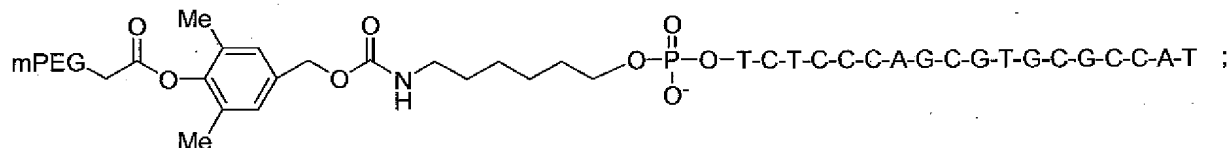
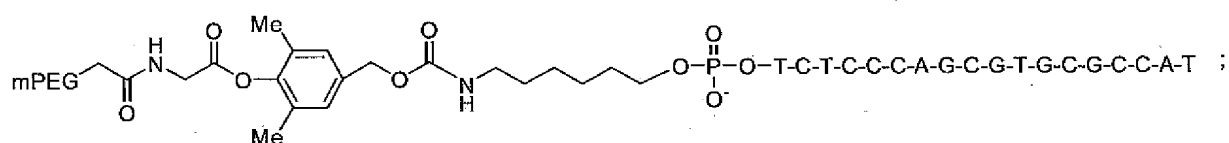
molecular weight of from about 3,000 Da to about 100,000 Da.

18. (Previously Presented) The prodrug of claim 27, wherein  $R_1$  has a weight average molecular weight of from about 5,000 Da to about 40,000 Da.

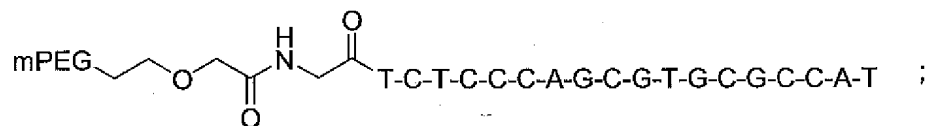
19. (Previously Presented) The prodrug of claim 8, wherein said antisense oligonucleotide is oblimersen (SEQ ID NO: 1).

20. (Cancelled)

21. (Currently Amended) The prodrug of claim 27 selected from the group consisting of:

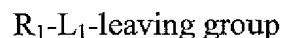


and

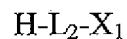


wherein all of which comprise an oligonucleotide of SEQ ID NO: 1.

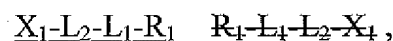
22. (Withdrawn/Currently Amended) A method of making a prodrug comprising:  
reacting a compound of the formula:



with a compound of the formula:



under conditions sufficient to form a prodrug of the formula



wherein:

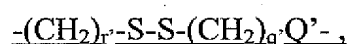
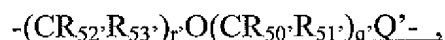
$R_1$  is a polyalkylene oxide polymer residue;

$L_1$  is a releasable linking moiety;

$L_2$  is a bifunctional spacing group comprising from about 2 to about 10 carbon atoms; and

$X_1$  is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides,

wherein  $L_2$  is selected from the group consisting of



wherein

$Q'$  is O, S or NH;

$R_{50'-53'}$  are independently selected from the group consisting of

hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,

aryl,  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy and  $C_{1-6}$  heteroalkoxy; and

$q'$  and  $r'$  are each a positive integer.

23-26. (Cancelled)

27. (Currently Amended) An oligonucleotide prodrug of the formula (†):



wherein:

$R_1$  is a polyalkylene oxide polymer residue;

$L_1$  a releasable linking moiety;

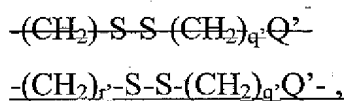
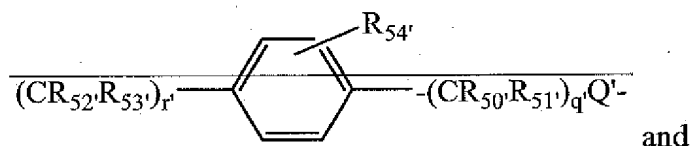
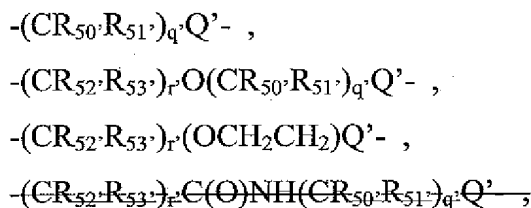
$L_2$  is a selected bifunctional spacing group comprising from about 2 to about 10 carbon atoms;

$X_1$  is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides;

n, and o are independently a positive integer; and  
provided that  $(o + n) \geq 2$ ,

wherein

$L_2$  is selected from the group consisting of:



wherein

$Q'$  is O, S or NH;

$R_{50'-53'}$  are independently selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cycloalkyls, aryls substituted aryls, aralkyls,  $C_{1-6}$  heteroalkyls, substituted  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy and  $C_{1-6}$  heteroalkoxy;

$R_{54'}$  is independently selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cycloalkyls, aryls substituted aryls, aralkyls,  $C_{1-6}$  heteroalkyls, substituted  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy,  $C_{1-6}$  heteroalkoxy,  $NO_2$ , haloalkyl and halogen; and

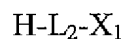
$q'$  and  $r'$  are each a positive integer.

28. (New) An oligonucleotide prodrug prepared by a process comprising:  
reacting a compound of the formula:

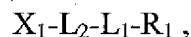
$R_1$ - $L_1$ -leaving group

with a compound of the formula:





under conditions sufficient to form a prodrug of the formula



wherein

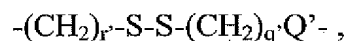
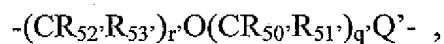
$\text{R}_1$  is a polyalkylene oxide;

$\text{L}_1$  is a releasable linking moiety;

$\text{L}_2$  is a bifunctional spacing group comprising from about 2 to about 10 carbon atoms; and

$\text{X}_1$  is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides,

wherein  $\text{L}_2$  is selected from the group consisting of:

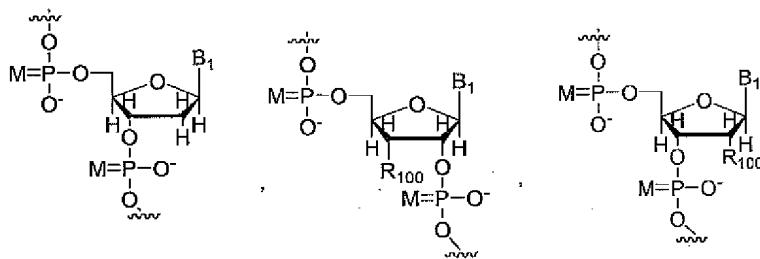


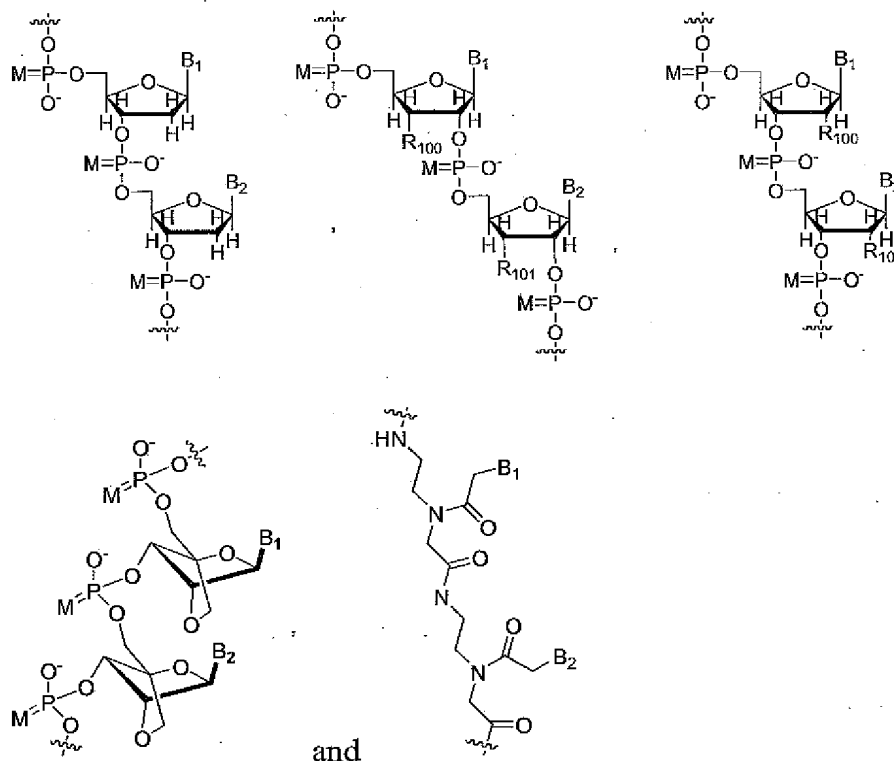
wherein

$\text{Q}'$  is O, S or NH;

$\text{R}_{50'}\text{-R}_{53'}$  are independently selected from the group consisting of hydrogen,  $\text{C}_{1-6}$  alkyls,  $\text{C}_{3-12}$  branched alkyls,  $\text{C}_{3-8}$  cycloalkyls, aryls,  $\text{C}_{1-6}$  heteroalkyls,  $\text{C}_{1-6}$  alkoxy, phenoxy and  $\text{C}_{1-6}$  heteroalkoxy; and  $q'$  and  $r'$  are each a positive integer.

29. (New) The prodrug of claim 28, wherein  $\text{X}_1$  comprises a nucleotide selected from the group consisting of





wherein

M is O or S;

B<sub>1</sub> and B<sub>2</sub> are independently selected from the group consisting of A (adenine), G (guanine), C (cytosine), T (thymine), U (uracil) and modified bases thereof;

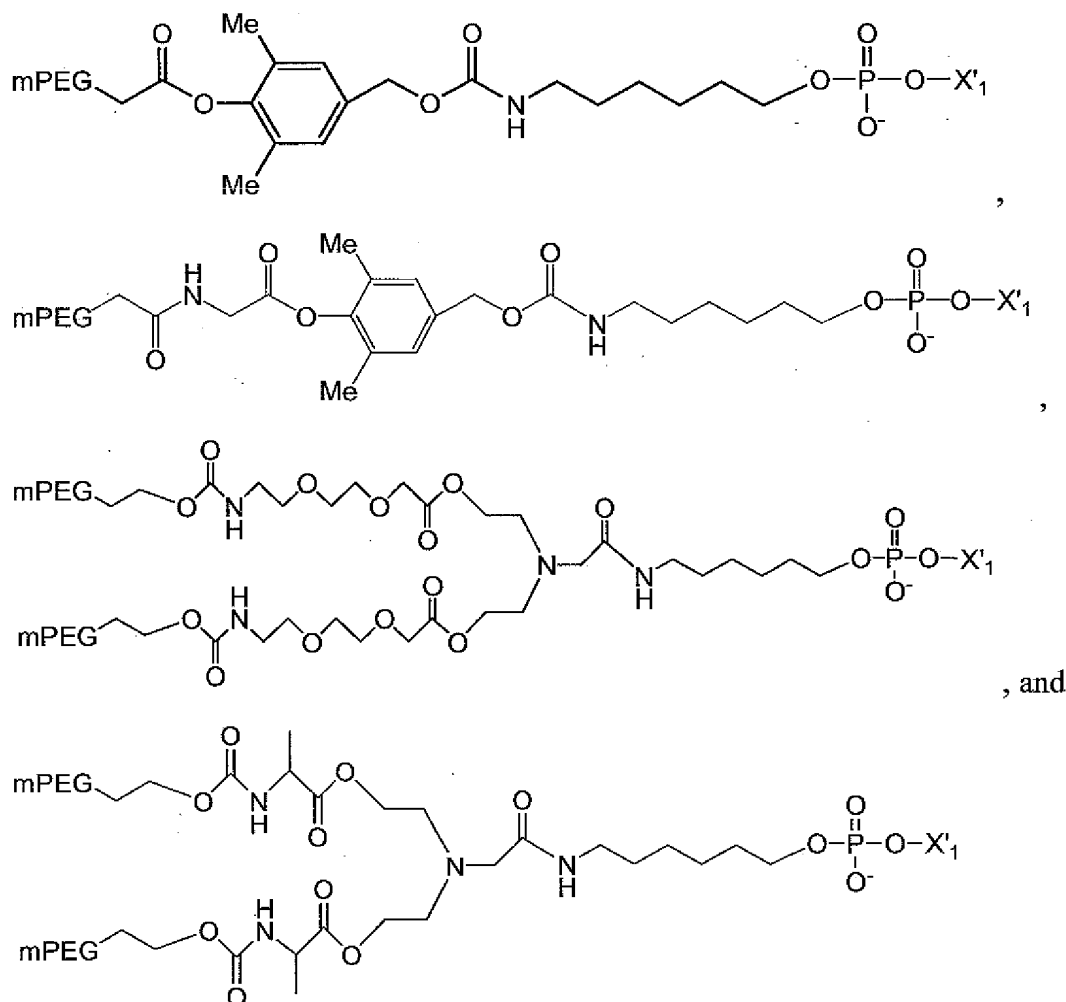
R<sub>100</sub> and R<sub>101</sub> are independently selected from the group consisting of H, OR' where R' is H, a C<sub>1-6</sub> alkyl, substituted alkyls, nitro, halo and aryl.

30. (New) The prodrug of claim 28, wherein X<sub>1</sub> is selected from the group consisting of oligonucleotides with phosphodiester backbones or phosphorothioate backbones, LNA, PNA, tricyclo-DNA, decoy ODN, ribozymes, spiegelmers, and CpG oligomers.

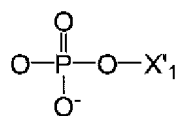
31. (New) The prodrug of claim 28, wherein X<sub>1</sub> includes a phosphorothioate backbone.

32. (New) The prodrug of claim 28, wherein X<sub>1</sub> is an antisense oligonucleotide.

33. (New) The prodrug of claim 32, wherein the antisense oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, wherein n of SEQ ID NO: 4 is any nucleotide.
34. (New) The prodrug of claim 28, wherein  $R_1$  is a polyalkylene glycol.
35. (New) The prodrug of claim 28, wherein  $R_1$  has a weight average molecular weight of from about 3,000 Da to about 100,000 Da.
36. (New) The prodrug of claim 34, wherein  $R_1$  has a weight average molecular weight of from about 5,000 Da to about 40,000 Da.
37. (New) The prodrug of claim 28 selected from the group consisting of



wherein



represents an oligonucleotide and point of terminal phosphate modification; and

mPEG is  $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_x$ , wherein x is a positive integer selected from about 10 to about 2300.